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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/807,897	03/24/2004	Rong Xiang	TSRI 874.1	6550

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
12/23/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/807,897	XIANG ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,26,28 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,26,28 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 March 2004 and 03 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's claim amendments filed on 08/19/2009 has been entered. Claims 2-25, 27, and 29-52 are cancelled. Claim 1 has been amended. Claims 1, 26, 28, and 53 are pending and currently under examination.

This application 10/807,897 filed on March 24, 2004 claims the benefit of 60/457,009 filed on 03/24/2003.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. Claims 1, 26, and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments filed on 08/19/2009.*

Claim 1 filed on 08/19/2009 reads as follows: An oral DNA vaccine suitable for eliciting an immune response against cancer cells in a human patient comprising a DNA construct operably encoding at least one human survivin protein and one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated Salmonella typhimurium vector that targets Peyer's patches in the gut, wherein the DNA vaccine induces acytotoxie T-lymphocyte immune response against tumor cells when orally administered to the patient.

Claim 26 reads as follows: The DNA vaccine of claim 1 wherein the DNA construct operably encoding *the* survivin protein comprises SEQ ID NO: 3.

Claim 53 reads as follows: The DNA vaccine of claim 1 wherein the DNA construct operably encoding *the* survivin protein comprises SEQ ID NO: 3, and wherein the DNA construct operably encoding the CCL21 cytokine comprises SEQ ID NO: 7.

It is noted that amended claim 1 recites "human survivin protein". However, the limitation "the DNA construct operably encoding the survivin protein comprises SEQ ID NO: 3" recited in claims 26 and 53 is the DNA encodes mouse survivin protein (See paragraph [0043] and page 19 listing of SEQ ID. No: 3, US 2004/0192631, publication of instant application). It is unclear what mammalian species of survivin proteins is/are encompassed by claims 1, 26, and 53.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

It is noted that ***Applicant's arguments*** and Examiner's ***Response to Applicant's arguments*** are documented at the end of the following four maintained 103 rejections.

2. Claim 1 remains rejected under 35 U.S.C. 103(a) as being unpatentable over **Haupt et al.** (Haupt et al., The potential of DNA vaccination against tumor-associated antigens for anti-tumor therapy, *Exp Biol Med (Maywood)*. 227(4):227-37, 2002) in view of **Gordan et al.** (Gordan et al. Universal tumor antigens as targets for immunotherapy, *Cytotherapy*, 4(4):317-27, 2002; this

reference has been cited in the office action mailed on 04/25/2008), **Andersen et al.** (Andersen et al., Spontaneous cytotoxic T-cell responses against survivin-derived MHC class I-restricted T-cell epitopes in situ as well as ex vivo in cancer patients, *Cancer Res.* 61(16):5964-8, 2001), **Luther et al.** (Luther et al., Differing activities of homeostatic chemokines CCL19, CCL21, and CXCL12 in lymphocyte and dendritic cell recruitment and lymphoid neogenesis, *J Immunol.* 169(1):424-33, 2002; this reference has been cited in the office action mailed on 07/06/2007), and **Lu et al.** (US 5,733,760, issued 03/31/1998; this reference has been cited in the office action mailed on 04/25/2008). Applicant's arguments filed 08/19/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 7-14 of the office action mailed on 05/26/2009.

For the clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 7-14 of the office action mailed on 05/26/2009, is reiterated below with revisions addressing claim amendments filed on 08/19/2009.

Amended claim 1 filed on 08/19/2009 reads as follows: A DNA vaccine suitable for eliciting an immune response against cancer cells in a human patient comprising a DNA construct operably encoding at least one human survivin protein and one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut, wherein the DNA vaccine induces a cytotoxic T-lymphocyte immune response against tumor cells when orally administered to a patient.

Claim interpretation: As discussed in rejection of claims 1, 26, and 53 under 35 U.S.C. 112 second, the limitation "survivin protein" recited in claim 1, is interpreted as either human survivin and/or mouse survivin.

Haupt et al. teaches that by DNA vaccination for a human cancer patient (See left column, page 228, Haupt et al., 2002), antigen-specific cellular as well as humoral immune responses can be generated. The induction of specific immune responses directed against antigens expressed in tumor cells and displayed e.g., by MHC class I complexes can inhibit tumor growth and lead to tumor rejection (See abstract, Figure1, Haupt et al., 2002). A common strategy to further enhance DNA-based immunization is to employ cytokine genes as adjuvants. (See Table 1, and right column, page 230, Haupt et al., 2002) by linking the cytokine gene directly to the DNA vaccine or inserting DNA coding for an immunomodulatory peptide of a cytokine (See left column, page 231, Haupt et al., 2002). As an example, Haupt et al. discloses that almost all of these carcinomas (i.e. a malignant tumor of epithelial origin) specifically express calcitonin, and calcitonin may represent a suitable target antigen for DNA vaccines. Haupt et al. shows that DNA immunization by gene gun with an expression plasmid encoding the human calcitonin precursor preprocalcitonin that enables induction of antigen-specific cellular and humoral immune responses in mice, and co-delivery of a plasmid encoding GM-CSF increases the efficacy of this DNA vaccine (See left column, page 233, Haupt et al., 2002).

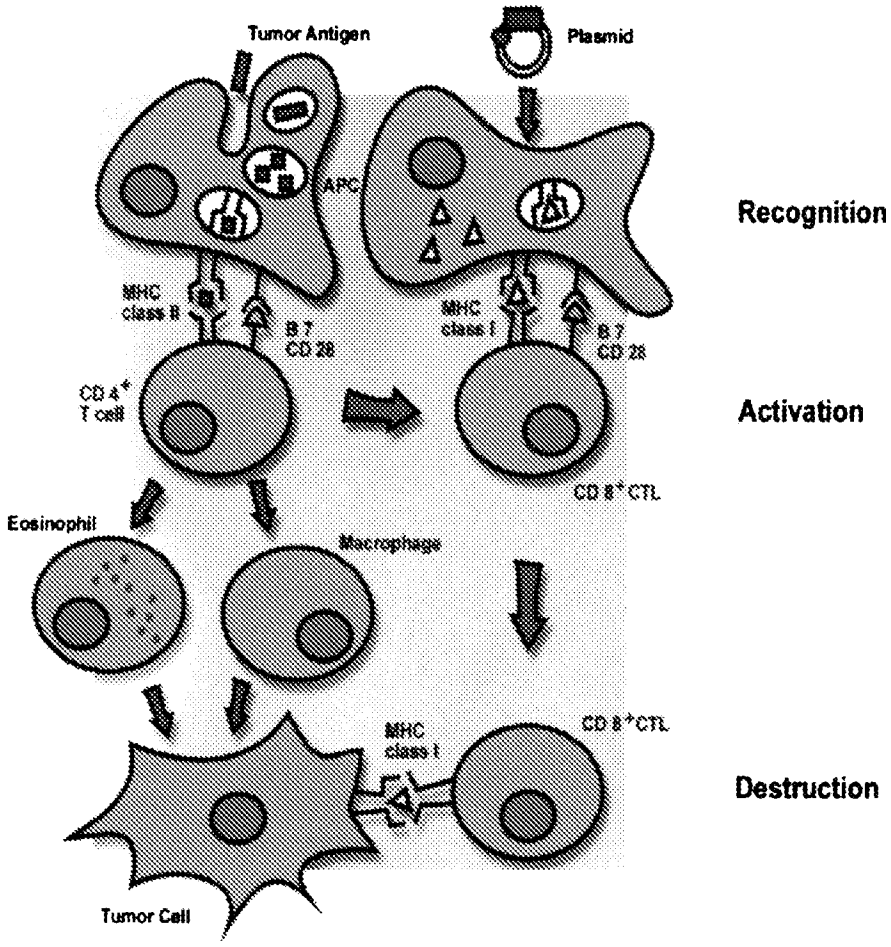

Figure 1. Priming of immune responses against tumor cells by DNA vaccination. The direct inoculation of plasmid DNA encoding a tumor-associated antigen into host cells, including professional APC, leads to the *in vivo* synthesis of the encoded antigen. The intracellular protein is processed into peptides that associate with MHC class I molecules. The MHC class I-peptide complex is displayed on the cell surface where it can be recognized by $CD8^+$ T cells. Once activated, $CD8^+$ T cells acquire cytotoxic functions and can specifically lyse cells expressing the target antigen. The predominant cell type capable of inducing T cells to become effector cells that can recognize and kill tumor cells following DNA immunization are bone marrow-derived APC. The CD28 molecule on the T cell membrane can interact with costimulatory molecules like B7-1 on APC. Lysis of transfected cells expressing the antigen or secretion of the antigen lead to the release of protein, which is taken up by APC. Internalized into lysosomes, the antigen is proteolytically degraded into peptides that associate with MHC class II molecules. The MHC class II-peptide complexes travel to the cell surface of APC where they can be recognized by $CD4^+$ T cells. These cells secrete cytokines that may facilitate tumor cell destruction in the effector phase of immune responses following DNA vaccination. Tumor-specific $CD4^+$ cells not only provide help for the induction of specific $CD8^+$ CTL, but may also be critical in activating macrophages and eosinophils to produce nitric oxide and superoxides that participate in the destruction of tumor cells.

Haupt et al. does not teach (i) survivin as a tumor specific antigen, (ii) CCL21 as a cytokine that enhance T cell mediated immune response, or (iii) a DNA construct been incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut.

However, at the time of filing of instant application, the art taught that (i) universal tumor antigens, including human survivin, expressed in all tumors but not expressed in non-cancerous tissue, can be used as targets immunotherapy, and (ii) the tumor cell specific immune response can be enhanced by the presence of various cytokines (See, for instance, second paragraph, right column of page 118, Gordan et al., 2002). Furthermore, the advantages of a vaccine comprising attenuated *Salmonella typhimurium* as a vector to express exogenous antigen(s) that can be delivered orally for vaccination and targets Peyer's patches in the gut, are also known in the art.

Regarding survivin being a universal tumor associated antigens as targets for immunotherapy, **Gordan et al.** teaches that the cardinal feature of universal tumor associated antigen (TAA, also known as tumor specific antigen) is that they are expressed in nearly all tumors but not expressed in non-cancerous tissue , and they are directly involved in the malignant phenotype of the tumor. Gordan et al. teaches that certain peptides derived from such Ags are expressed on the tumor-cell surface, as evidenced by Ag-specific, MHC-restricted T-cell anti-tumor reactivity. Gordan et al. also teaches that four examples (i.e. a definitive number) of universal tumor Ags (hTERT, CYP1B1, survivin, and MDM2; see left column page 321 and Table 1 page 3232), each at various levels of preclinical and clinical development. Gordan et al. further teaches that features of universal TAA indicate a pre-existing, high-affinity T-cell pool

that can be activated *in vivo* in patients, without immunoselection of variant tumor cells no longer expressing the Ag of choice. (See summary of Results and Discussion, page 317, Gordan et al. Universal tumor antigens as targets for immunotherapy, *Cytotherapy*, 4(4):317-27, 2002). Consistent with the teachings of Gordan et al., **Andersen et al.** teaches that advances in therapeutic tumor vaccinations necessitate the identification of broadly expressed, immunogenic tumor antigens that are not prone to immune selection. To this end, the human inhibitor of apoptosis, survivin, is a prime candidate because it is expressed in most human neoplasms but not in normal, differentiated tissues. Anderson et al. demonstrates spontaneous cytotoxic T-cell responses against survivin-derived MHC class I-restricted T-cell epitopes in breast cancer, leukemia, and melanoma patients both *in situ* as well as *ex vivo* (See abstract, Andersen et al., 2001).

Regarding CCL21/SLC (secondary lymphoid tissue chemokine) as a cytokine that specifically enhances T cell mediated immune response, **Luther et al.** teaches that a comparison of CCL19 transgenic mice with mice expressing CCL21 (secondary lymphoid tissue chemokine) revealed that CCL21 induced larger and more organized infiltrates, and a more significant role for CCL21 is also suggested in lymphoid tissues, as CCL21 protein was found to be present in lymph nodes and spleen at much higher concentrations than CCL19 (See abstract, Luther et al., 2002). Luther et al. teaches that a striking feature of the infiltrates in RIP-CCL21 transgenic mice was the localization of DCs and T cells, but not B cells, close to the chemokine-expressing islet cells., which is exactly the opposing pattern has been previously observed in RIP-CXCL13 transgenic mice, where B cells line the islets and T cells are localized more distantly (See second paragraph, left column, page 426, Luther et al., 2002).

Regarding the limitation "DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut", **Lu et al.** (1998) teaches the following: Attenuated *Salmonella typhimurium* has been proposed as one means of providing effective delivery of desired antigens. They provide the advantage that they can be delivered orally. The bacteria grow rapidly and do not require growth in cell culture. Thus, large scale production of vectors, for example, in the use of vaccines, can be accomplished more quickly and easy then where mammalian tissue cultures are required. After oral ingestion, *Salmonella* are concentrated within the liver, spleen, bone marrow, and the Peyers' patches of the gut-associated lymphoid tissue (GALT) (See Abstract, and lines 39-54, column 1, Lu et al., 1998).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to generate a DNA vaccine construct to be incorporated into and orally delivered by *Salmonella* vector, as taught by Lu et al (1998), via combined teachings of (i) Haupt et al regarding the induction of specific immune responses directed against antigens expressed in human tumor cells and displayed e.g., by MHC class I complexes via DNA vaccination of tumor specific antigen and cytokine, (ii) Gordan et al. regarding survivin is one of four of universal tumor Ags (hTERT, CYP1B1, survivin, and MDM2), and Andersen et al. regarding spontaneous cytotoxic T-cell responses against survivin-derived MHC class I-restricted T-cell epitopes in breast cancer, leukemia, and melanoma patients both *in situ* as well as *ex vivo,* and (iii) Luther et al. regarding cytokine CCL21 specifically enhances T cell mediated immune response, to arrive at the claimed DNA vaccine that induces a cytotoxic T lymphocyte immune response against tumor cells when orally administering *Salmonella typhimurium* comprising the DNA vaccine to a patient.

One having ordinary skill in the art would have been motivated to combine the teachings of Haupt et al. (2002) in view of Gordan et al. (2002), Andersen et al. (2001), Luther et al. (2002), and Lu et al. (1998) to achieve at a DNA vaccine that induces s cytotoxic T lymphocyte immune response against all tumors because (i) Haupt et al. teaches a DNA vaccine that induces cytotoxic T lymphocyte immune response by expressing various tumor associated antigens (TAAs), which are present in various tumors (i.e. non-universal TAA), and the effect of expression of cytokine in enhancing the efficacy of the DNA vaccine, (ii) Gordan et al. teaches survivin is one of four established universal tumor Ags (hTERT, CYP1B1, survivin, and MDM2), and Andersen et al. regarding spontaneous cytotoxic T-cell responses against survivin-derived MHC class I-restricted T-cell epitopes in breast cancer, leukemia, and melanoma patients both *in situ* as well as *ex vivo*, (iii) Luther et al. teaches cytokine CCL21, not cytokine CCL19, specifically enhances T cell mediated immune response, and (iv) Lu et al. teaches that the advantage of using *Salmonella typhimurium* comprising the DNA vaccine as a vehicle for targeted delivery of antigen to Peyer's paches in the gut via oral delivery of *S. typhimurium*

There would have been a reasonable expectation of success given (i) successful demonstration of DNA vaccine delivered by gene gun with an expression plasmid encoding the human calcitonin precursor preprocalcitonin enables induction of antigen-specific cellular and humoral immune responses in mice, and co-delivery of a plasmid encoding GM-CSF increased the efficacy of this DNA vaccine, by the teachings of Haupt et al., (ii) successful identification and validation of survivin as one of four universal tumor associated antigens, by the teachings of Gordan et al., and demonstration of spontaneous cytotoxic T-cell responses against survivin-derived MHC class I-restricted T-cell epitopes in breast cancer, leukemia, and melanoma patients

both *in situ* as well as *ex vivo,* by the teachings of Andersen et al., and (iii) successful demonstration of the effect of CCL21 in specifically increasing T cell mediated cytolytic response, by the teachings of Luther et al., and (iv) successful generation of attenuated *Salmonella typhimurium* that can express exogenous antigens and the demonstration of using attenuated *Salmonella typhimurium* for oral vaccination, by the teachings of Lu et al., 1998.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

3. Claim 26 remains rejected under 35 U.S.C. 103(a) as being unpatentable over **Haupt et al**. (Haupt et al., The potential of DNA vaccination against tumor-associated antigens for antitumor therapy, *Exp Biol Med (Maywood)*. 227(4):227-37, 2002) in view of **Gordan et al.** (Gordan et al. Universal tumor antigens as targets for immunotherapy, *Cytotherapy*, 4(4):317-27, 2002; this reference has been cited in the office action mailed on 04/25/2008), **Andersen et al.** (Andersen et al., Spontaneous cytotoxic T-cell responses against survivin-derived MHC class I-restricted T-cell epitopes in situ as well as ex vivo in cancer patients, *Cancer Res.* 61(16):5964-8, 2001), **Luther et al.** (Luther et al., Differing activities of homeostatic chemokines CCL19, CCL21, and CXCL12 in lymphocyte and dendritic cell recruitment and lymphoid neogenesis, *J Immunol.* 169(1):424-33, 2002; this reference has been cited in the office action mailed on 07/06/2007), and **Lu et al.** (US 5,733,760, issued 03/31/1998; this reference has been cited in the office action mailed on 04/25/2008), as applied to claim 1 above, and further in view of **Bennett et al.** (Bennett et al. WO200157059-A1 and U.S. Patent No. 6,335,194, SEQ ID No: 10, columns 27, 53-55; this reference has been provided in the Non-Final office action mailed on 12/13/2006). Applicant's arguments filed 08/19/2009 have been fully considered and they are not

persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 14-18 of the office action mailed on 05/26/2009.

For the clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 14-18 of the office action mailed on 05/26/2009, is reiterated below with revisions addressing claim amendments filed on 08/19/2009.

Claim 1 filed on 08/19/2009 reads as follows: An oral DNA vaccine suitable for eliciting an immune response against cancer cells in a human patient comprising a DNA construct operably encoding at least one human survivin protein and one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut, wherein the DNA vaccine induces a cytotoxic T-lymphocyte immune response against tumor cells when orally administered to the patient.

Claim 26 reads as follows: The DNA vaccine of claim 1 wherein the DNA construct operably encoding *the* survivin protein comprises SEQ ID NO: 3.

Claim interpretation: As discussed in the rejection of 1 and 26 are rejected under 35 U.S.C. 112, second paragraph, claim 1 recites human survivin protein, but SEQ ID No:3 recited in claim 26 is the DNA encodes mouse survivin. Claim 26 is interpreted to encompass human survivin protein and/or mouse survivin protein.

The teachings of Haupt et al., Gordan et al., Andersen et al., Luther et al., and Lu et al. have been discussed in the preceding section of the rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over Haupt et al. (2002) in view of Gordan et al. (2002), Andersen et al. (2001), Luther et al. (2002), and Lu et al. (1998).

None of Haupt et al., Gordan et al., Andersen et al., Luther et al., and Lu et al. teaches SEQ ID No: 3 recited in claim 26.

However, at the time of filing of instant application, the DNA construct encoding a murine survivin protein comprising SEQ ID No. 3 recited in claim 26, was known in the art. For instant, **Bennett et al.** teach DNA encoding mouse survivin that identical to SEQ ID NO: 3 (See Bennett et al. WO200157059-A1 and U.S. Patent No. 6,335,194, SEQ ID No: 10, columns 27, 53-55, detailed alignment of sequences listed below)

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RESULT 1

AAS21530
ID   AAS21530 standard; cDNA; 955 BP.
XX
AC   AAS21530;
XX
DT   21-NOV-2001  (first entry)
XX
DE   DNA encoding mouse survivin.
XX
KW   Survivin; human; mouse; cytostatic; antisense oligonucleotide;
KW   hyperproliferative condition; cancer; apoptosis; cytokinesis; ss.
XX
OS   Mus musculus.
XX
PN   WO200157059-A1.
XX
PD   09-AUG-2001.
XX
PF   30-JAN-2001; 2001WO-US002939.
XX
PR   02-FEB-2000; 2000US-00496694.
XX
PA   (ISIS-) ISIS PHARM INC.
XX
PI   Bennett CF,  Ackermann EJ,  Swayze EE,  Cowsert LM;
XX
DR   WPI; 2001-488863/53.
XX
PT   Novel antisense compounds for modulating the expression of Survivin and
PT   treatment of cancer.
XX
PS   Example 13; Page 80-81; 120pp; English.
XX
CC   The invention relates to antisense oligonucleotides targeted to a nucleic
CC   acid molecule encoding human Survivin, where the antisense
CC   oligonucleotide inhibits the expression of human Survivin. These
CC   antisense oligonucleotides are used in the treatment of an animal
CC   suffering from a disease or condition associated with Survivin, e.g. a
CC   hyperproliferative condition such as cancer, and comprises administering
CC   a therapeutically or prophylactically effective amount of the antisense
CC   oligonucleotide so that expression of Survivin is inhibited. The
CC   oligonucleotides can also be used to treat a human suffering from a
CC   disease or condition characterised by a reduction in apoptosis comprising
CC   administering the antisense oligonucleotide to a human. In addition, the
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CC   antisense oligonucleotide and a cytotoxic chemotherapeutic agent e.g.
CC   taxol or cisplatin, can be used to modulate apoptosis, cytokinesis or the
CC   cell cycle, or inhibit the proliferation in a cancer cell by contacting
CC   the cell with the antisense oligonucleotide. AAS21521-AAS21768 represent
CC   Survivin nucleic acids, and antisense oligonucleotides targeted to
CC   Survivin, used in the method of the invention
XX
SQ   Sequence 955 BP; 230 A; 227 C; 265 G; 233 T; 0 U; 0 Other;

  Query Match             100.0%;  Score 955;  DB 5;  Length 955;
  Best Local Similarity   100.0%;  Pred. No. 3.6e-284;
  Matches  955;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GGCACGAGGGGGCCGGGGCTCTCCCGGCATGCTCTGCGGCGCGCCTCCGCCCGCGCGATT 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GGCACGAGGGGGCCGGGGCTCTCCCGGCATGCTCTGCGGCGCGCCTCCGCCCGCGCGATT 60

Qy         61 TGAATCCTGCGTTTGAGTCGTCTTGGCGGAGGTTGTGGTGACGCCATCATGGGAGCTCCG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TGAATCCTGCGTTTGAGTCGTCTTGGCGGAGGTTGTGGTGACGCCATCATGGGAGCTCCG 120

Qy        121 GCGCTGCCCCAGATCTGGCAGCTGTACCTCAAGAACTACCGCATCGCCACCTTCAAGAAC 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 GCGCTGCCCCAGATCTGGCAGCTGTACCTCAAGAACTACCGCATCGCCACCTTCAAGAAC 180

Qy        181 TGGCCCTTCCTGGAGGACTGCGCCTGCACCCCAGAGCGAATGGCGGAGGCTGGCTTCATC 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 TGGCCCTTCCTGGAGGACTGCGCCTGCACCCCAGAGCGAATGGCGGAGGCTGGCTTCATC 240

Qy        241 CACTGCCCTACCGAGAACGAGCCTGATTTGGCCCAGTGTTTTTTCTGCTTTAAGGAATTG 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 CACTGCCCTACCGAGAACGAGCCTGATTTGGCCCAGTGTTTTTTCTGCTTTAAGGAATTG 300

Qy        301 GAAGGCTGGGAACCCGATGACAACCCGATAGAGGAGCATAGAAAGCACTCCCCTGGCTGC 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 GAAGGCTGGGAACCCGATGACAACCCGATAGAGGAGCATAGAAAGCACTCCCCTGGCTGC 360

Qy        361 GCCTTCCTCACTGTCAAGAAGCAGATGGAAGAACTAACCGTCAGTGAATTCTTGAAACTG 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 GCCTTCCTCACTGTCAAGAAGCAGATGGAAGAACTAACCGTCAGTGAATTCTTGAAACTG 420

Qy        421 GACAGACAGAGAGCCAAGAACAAAATTGCAAAGGAGACCAACAACAAGCAAAAAGAGTTT 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 GACAGACAGAGAGCCAAGAACAAAATTGCAAAGGAGACCAACAACAAGCAAAAAGAGTTT 480

Qy        481 GAAGAGACTGCAAAGACTACCCGTCAGTCAATTGAGCAGCTGGCTGCCTAATGCTGAGCC 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 GAAGAGACTGCAAAGACTACCCGTCAGTCAATTGAGCAGCTGGCTGCCTAATGCTGAGCC 540

Qy        541 TTTGCTGAGATAACTTGGACCTGAGTGACATGCCACATCTAAGCCACGCATCCCAGCTTT 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 TTTGCTGAGATAACTTGGACCTGAGTGACATGCCACATCTAAGCCACGCATCCCAGCTTT 600

Qy        601 TCCAGCCAGGGCCTCCTAGCAGGATCTTAGAGAAGGAGACAGTGGTATTTTGAAACTGGA 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 TCCAGCCAGGGCCTCCTAGCAGGATCTTAGAGAAGGAGACAGTGGTATTTTGAAACTGGA 660

Qy        661 TATCAAATATTTTTGGTTTTGCTTTAAAGTGGCTACCTCTCTTTGGTTTTGTGGCTTTGC 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        661 TATCAAATATTTTTGGTTTTGCTTTAAAGTGGCTACCTCTCTTTGGTTTTGTGGCTTTGC 720

Qy        721 TCTATTGTGACGTGGACTTAAGCAATAAGGAAGTGATGAAGGGACAGTGTTCTCTGACAG 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        721 TCTATTGTGACGTGGACTTAAGCAATAAGGAAGTGATGAAGGGACAGTGTTCTCTGACAG 780

Qy        781 GACCTGTGGGGGTCGGGGTGCCTGTGCAAGGTCTTGGTTCTGATTGTGATATTTCCATAC 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db        781 GACCTGTGGGGGTCGGGGTGCCTGTGCAAGGTCTTGGTTCTGATTGTGATATTTCCATAC 840

Qy        841 AGGGCTGCTAATGCAGCCCATGGGTAAGTGTGGTTATATGTGTTTGTGCTGATAATTTTG 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        841 AGGGCTGCTAATGCAGCCCATGGGTAAGTGTGGTTATATGTGTTTGTGCTGATAATTTTG 900

Qy        901 TCCTGATGAGTTTTCCTACCACGGGGTAACGGAATAAAATCACTTGAAAAAGTGG 955
              |||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        901 TCCTGATGAGTTTTCCTACCACGGGGTAACGGAATAAAATCACTTGAAAAAGTGG 955
```

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Bennett et al. on the DNA encoding mouse survivin, which is identical to SEQ ID NO: 3 recited in claim 26 of instant application, into the combined teachings of Haupt et al., Gordan et al., Andersen et al., Luther et al., and Lu et al. directing to a DNA vaccine suitable for eliciting a CTL immune response against cancer cells comprising a DNA construct operably encoding at least one survivin protein and at least one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut of a patient when the patient is orally vaccinated with the DNA construct.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Bennett et al. on the DNA encoding mouse survivin, which is identical to SEQ ID NO: 3 recited in claim 26 of instant application, into the combined teachings of Haupt et al., Gordan et al., Andersen et al., Luther et al., and Lu et al. because survivin is conserved in mammals, universally expressed in tumor cells but not in other normal tissues, and SEQ ID No: 3 encodes mouse survivin.

There would have been a reasonable expectation of success given (i) successful demonstration of DNA vaccine delivered by gene gun with an expression plasmid encoding the human calcitonin precursor preprocalcitonin enables induction of antigen-specific cellular and

humoral immune responses in mice, and co-delivery of a plasmid encoding GM-CSF increased the efficacy of this DNA vaccine, by the teachings of Haupt et al., (ii) successful identification and validation of survivin as one of four universal tumor associated antigens, by the teachings of Gordan et al. and demonstration of spontaneous cytotoxic T-cell responses against survivin-derived MHC class I-restricted T-cell epitopes in breast cancer, leukemia, and melanoma patients both *in situ* as well as *ex vivo,* by the teachings of Andersen et al., and (iii) successful demonstration of the effect of CCL21 in specifically increasing T cell mediated cytolytic response, by the teachings of Luther et al., and (iv) successful generation of attenuated *Salmonella typhimurium* that can express exogenous antigens and the demonstration of using attenuated *Salmonella typhimurium* for oral vaccination, by the teachings of Lu et al., 1998, and (v) DNA encoding mouse survivin was readily available by the teachings of Bennett et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

4. Claim 28 remains rejected under 35 U.S.C. 103(a) as being unpatentable over **Haupt et al**. (Haupt et al., The potential of DNA vaccination against tumor-associated antigens for antitumor therapy, *Exp Biol Med (Maywood)*. 227(4):227-37, 2002) in view of **Gordan et al.** (Gordan et al. Universal tumor antigens as targets for immunotherapy, *Cytotherapy*, 4(4):317-27, 2002; this reference has been cited in the office action mailed on 04/25/2008), **Andersen et al.** (Andersen et al., Spontaneous cytotoxic T-cell responses against survivin-derived MHC class I-restricted T-cell epitopes in situ as well as ex vivo in cancer patients, *Cancer Res.* 61(16):5964-8, 2001), **Luther et al.** (Luther et al., Differing activities of homeostatic chemokines CCL19, CCL21, and CXCL12 in lymphocyte and dendritic cell recruitment and lymphoid neogenesis, *J*

Immunol. 169(1):424-33, 2002; this reference has been cited in the office action mailed on 07/06/2007), and **Lu et al.** (US 5,733,760, issued 03/31/1998; this reference has been cited in the office action mailed on 04/25/2008), as applied to claim 1 above, and further in view of **Tanabe et al.** (Tanabe et al., direct submission, submitted to Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA, on 03-JUN-1997, direct submission of DNA sequences of CCL21; this reference has been provided in the Non-Final office action mailed on 12/13/2006). Applicant's arguments filed 08/19/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 19-22 of the office action mailed on 05/26/2009.

For the clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 19-22 of the office action mailed on 05/26/2009, is reiterated below with revisions addressing claim amendments filed on 08/19/2009.

The teachings of Haupt et al., Gordan et al., Andersen et al., Luther et al., and Lu et al. have been discussed in the preceding section of the rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over Haupt et al. (2002) in view of Gordan et al. (2002), Andersen et al. (2001), Luther et al. (2002), and Lu et al. (1998).

None of Haupt et al., Gordan et al., Andersen et al., Luther et al., and Lu et al. teaches SEQ ID No:7 recited in claim 28.

However, at the time of filing of instant application, the DNA construct encoding a murine survivin protein comprising SEQ ID No. 7 recited in claim 28, was known in the art. For instant, **Tanabe et al.** teach DNA encoding mouse CCL21 that is identical SEQ ID NO: 7

(Tanabe et al., direct submission, submitted to Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA, on 03-JUN-1997, detailed alignment of sequences listed below; this reference has been provided in the Non-Final office action mailed on 12/13/2006).

```
RESULT 1
AF006637
LOCUS       AF006637                615 bp    mRNA    linear   ROD 22-JUN-1997
DEFINITION  Mus musculus beta-chemokine TCA4 mRNA, complete cds.
ACCESSION   AF006637
VERSION     AF006637.1  GI:2209188
KEYWORDS    .
SOURCE      Mus musculus (house mouse)
  ORGANISM  Mus musculus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia;
            Sciurognathi; Muroidea; Muridae; Murinae; Mus.
REFERENCE   1  (bases 1 to 615)
  AUTHORS   Tanabe,S., Lu,Z., Luo,Y., Quackenbush,E.J., Berman,M.A.,
            Collins-Racie,L.A., Mi,S., Reilly,C., Lo,D., Jacobs,K.A. and
            Dorf,M.E.
  TITLE     Direct Submission
  JOURNAL   Submitted (03-JUN-1997) Genetics Institute, 87 Cambridge Park
            Drive, Cambridge, MA 02140, USA
FEATURES             Location/Qualifiers
     source          1. .615
                     /organism="Mus musculus"
                     /mol_type="mRNA"
                     /db_xref="taxon:10090"
                     /tissue_type="thymus"
                     /dev_stage="adult"
     CDS             97. .498
                     /note="beta-chemokine"
                     /codon_start=1
                     /product="TCA4"
                     /protein_id="AAB61440.1"
                     /db_xref="GI:2209189"
                     /translation="MAQMMTLSLLSLVLALCIPWTQGSDGGGQDCCLKYSQKKIPYSI
                     VRGYRKQEPSLGCPIPAILFSPRKHSKPELCANPEEGWVQNLMRRLDQPPAPGKQSPG
                     CRKNRGTSKSGKKGKGSKGCKRTEQTQPSRG"
ORIGIN

  Query Match             100.0%;  Score 615;  DB 6;  Length 615;
  Best Local Similarity   100.0%;  Pred. No. 3e-193;
  Matches  615;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GAATTCGGCCAAAGAGGCCTACGGCCAAAGAGGGCTAAACTTGCGGCTGTCCATCTCACC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GAATTCGGCCAAAGAGGCCTACGGCCAAAGAGGGCTAAACTTGCGGCTGTCCATCTCACC 60

Qy         61 TACAGCTCTGGTCTCATCCTCAACTCAACCACAATCATGGCTCAGATGATGACTCTGAGC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TACAGCTCTGGTCTCATCCTCAACTCAACCACAATCATGGCTCAGATGATGACTCTGAGC 120

Qy        121 CTCCTTAGCCTGGTCCTGGCTCTCTGCATCCCCTGGACCCAAGGCAGTGATGGAGGGGGT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 CTCCTTAGCCTGGTCCTGGCTCTCTGCATCCCCTGGACCCAAGGCAGTGATGGAGGGGGT 180

Qy        181 CAGGACTGCTGCCTTAAGTACAGCCAGAAGAAAATTCCCTACAGTATTGTCCGAGGCTAT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 CAGGACTGCTGCCTTAAGTACAGCCAGAAGAAAATTCCCTACAGTATTGTCCGAGGCTAT 240
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Qy        241 AGGAAGCAAGAACCAAGTTTAGGCTGTCCCATCCCGGCAATCCTGTTCTCACCCCGGAAG 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 AGGAAGCAAGAACCAAGTTTAGGCTGTCCCATCCCGGCAATCCTGTTCTCACCCCGGAAG 300

Qy        301 CACTCTAAGCCTGAGCTATGTGCAAACCCTGAGGAAGGCTGGGTGCAGAACCTGATGCGC 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 CACTCTAAGCCTGAGCTATGTGCAAACCCTGAGGAAGGCTGGGTGCAGAACCTGATGCGC 360

Qy        361 CGCCTGGACCAGCCTCCAGCCCCAGGGAAACAAAGCCCCGGCTGCAGGAAGAACCGGGGA 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 CGCCTGGACCAGCCTCCAGCCCCAGGGAAACAAAGCCCCGGCTGCAGGAAGAACCGGGGA 420

Qy        421 ACCTCTAAGTCTGGAAAGAAAGGAAAGGGCTCCAAGGGCTGCAAGAGAACTGAACAGACA 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 ACCTCTAAGTCTGGAAAGAAAGGAAAGGGCTCCAAGGGCTGCAAGAGAACTGAACAGACA 480

Qy        481 CAGCCCTCAAGAGGATAGCCCAGTAGCCCGCCTGGAGCCCAGGAGATCCCCCACGAACTT 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 CAGCCCTCAAGAGGATAGCCCAGTAGCCCGCCTGGAGCCCAGGAGATCCCCCACGAACTT 540

Qy        541 CAAGCTGGGTGGTTCACGGTCCAACTCACAGGCAAAGAGGGAGCTAGAAAACAGACTCAG 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 CAAGCTGGGTGGTTCACGGTCCAACTCACAGGCAAAGAGGGAGCTAGAAAACAGACTCAG 600

Qy        601 GAGCCGCTAGTCGAG 615
              |||||||||||||||
Db        601 GAGCCGCTAGTCGAG 615
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Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Tanabe et al. on the DNA encoding mouse survivin, which is identical to SEQ ID NO: 7 recited in claim 28 of instant application, into the combined teachings of Haupt et al., Gordan et al., Anderson et al., Luther et al., and Lu directing to a DNA vaccine suitable for eliciting a CTL immune response against cancer cells comprising a DNA construct operably encoding at least one survivin protein and at least one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut of a patient when the patient is orally vaccinated with the DNA construct.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Tanabe et al. on the DNA encoding mouse surviving, which is identical to SEQ ID NO: 7 recited in claim 28 of instant application, into the combined teachings of Haupt et al.,

Gordan et al., Andersen et al., Luther et al., and Lu et al. because cytokine CCL21 is known to specifically enhance T cell mediated immune response, and SEQ ID No: 7 encodes mouse CCL21.

There would have been a reasonable expectation of success given (i) successful demonstration of DNA vaccine delivered by gene gun with an expression plasmid encoding the human calcitonin precursor preprocalcitonin enables induction of antigen-specific cellular and humoral immune responses in mice, and co-delivery of a plasmid encoding GM-CSF increased the efficacy of this DNA vaccine, by the teachings of Haupt et al., (ii) successful identification and validation of survivin as one of four universal tumor associated antigens, by the teachings of Gordan et al. and demonstration of spontaneous cytotoxic T-cell responses against survivin-derived MHC class I-restricted T-cell epitopes in breast cancer, leukemia, and melanoma patients both *in situ* as well as *ex vivo,* by the teachings of Andersen et al., and (iii) successful demonstration of the effect of CCL21 in specifically increasing T cell mediated cytolytic response, by the teachings of Luther et al., and (iv) successful generation of attenuated *Salmonella typhimurium* that can express exogenous antigens and the demonstration of using attenuated *Salmonella typhimurium* for oral vaccination, by the teachings of Lu et al., 1998, and (v) DNA encoding mouse CCL21 was readily available by the teachings of Tanabe et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

5. Claim 53 remains rejected under 35 U.S.C. 103(a) as being unpatentable over **Haupt et al**. (Haupt et al., The potential of DNA vaccination against tumor-associated antigens for antitumor therapy, *Exp Biol Med (Maywood)*. 227(4):227-37, 2002) in view of **Gordan et al.**

(Gordan et al. Universal tumor antigens as targets for immunotherapy, *Cytotherapy*, 4(4):317-27, 2002; this reference has been cited in the office action mailed on 04/25/2008), **Andersen et al.** (Andersen et al., Spontaneous cytotoxic T-cell responses against survivin-derived MHC class I-restricted T-cell epitopes in situ as well as ex vivo in cancer patients, *Cancer Res.* 61(16):5964-8, 2001), **Luther et al.** (Luther et al., Differing activities of homeostatic chemokines CCL19, CCL21, and CXCL12 in lymphocyte and dendritic cell recruitment and lymphoid neogenesis, *J Immunol.* 169(1):424-33, 2002; this reference has been cited in the office action mailed on 07/06/2007), and **Lu et al.** (US 5,733,760, issued 03/31/1998; this reference has been cited in the office action mailed on 04/25/2008), as applied to claim 1 above, and further in view of **Bennett et al.** (Bennett et al. WO200157059-A1 and U.S. Patent No. 6,335,194, SEQ ID No: 10, columns 27, 53-55; this reference has been provided in the Non-Final office action mailed on 12/13/2006), and **Tanabe et al.** (Tanabe et al., direct submission, submitted to Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA, on 03-JUN-1997, direct submission of DNA sequences of CCL21; this reference has been provided in the Non-Final office action mailed on 12/13/2006). Applicant's arguments filed 08/19/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 19-22 of the office action mailed on 05/26/2009.

For the clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 19-22 of the office action mailed on 05/26/2009, is reiterated below with revisions addressing claim amendments filed on 08/19/2009.

Claim 1 filed on 08/19/2009 reads as follows: An oral DNA vaccine suitable for eliciting an immune response against cancer cells in a human patient comprising a DNA construct

operably encoding at least one human survivin protein and one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated Salmonella typhimurium vector that targets Peyer's patches in the gut, wherein the DNA vaccine induces acytotoxie T-lymphocyte immune response against tumor cells when orally administered to the patient.

Claim 53 reads as follows: The DNA vaccine of claim 1 wherein the DNA construct operably encoding *the* survivin protein comprises SEQ ID NO: 3, and wherein the DNA eonstruet operably encoding the CCL21 cytokine comprises SEQ ID NO: 7.

Claim interpretation: As discussed in the rejection of 1, 26, and 53 are rejected under 35 U.S.C. 112, second paragraph, claim 1 recites human survivin protein, but SEQ ID No:3 recited in claim 26 is the DNA encodes mouse survivin. Claim 53 is interpreted to encompass human survivin protein and/or mouse survivin protein.

The teachings of Haupt et al., Gordan et al., Andersen et al., Luther et al., and Lu et al. have been discussed in the preceding section of the rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over Haupt et al. (2002) in view of Gordan et al. (2002), Andersen et al. (2001), Luther et al. (2002), and Lu et al. (1998).

None of Haupt et al., Gordan et al., Andersen et al., Luther et al., and Lu et al. teaches SEQ ID No:3 and SEQ ID No: 7 recited in claim 53.

However, at the time of filing of instant application, the DNA construct encoding a murine survivin protein comprising SEQ ID No. 3, the DNA construct encoding mouse CCL21 comprising SEQ ID No: 7, recited in claim 53, were known in the art. For instant, Bennett et al. teach DNA encoding mouse survivin that identical to SEQ ID NO: 3 (See Bennett et al. WO200157059-A1 and U.S. Patent No. 6,335,194, SEQ ID No: 10, columns 27, 53-55, see detailed alignment of sequences listed in the preceding rejection #7), and Tanabe et al. teach

DNA encoding mouse CCL21 that is identical SEQ ID NO: 7 (Tanabe et al., direct submission, submitted to Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA, on 03-JUN-1997, detailed alignment of sequences listed in the preceding rejection #8)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Bennett et al. on the DNA encoding mouse survivin, which is identical to SEQ ID NO: 3, and the teachings of Tanabe et al. on the DNA encoding mouse CCL21, which is identical to SEQ ID NO: 7, as recited in claim 53 of instant application, into the combined teachings of Haupt et al., Gordan et al., Andersen et al., Luther et al., and Lu et al., directing to a DNA vaccine suitable for eliciting a CTL immune response against cancer cells comprising a DNA construct operably encoding at least one survivin protein and at least one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut of a patient when the patient is orally vaccinated with the DNA construct.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Bennett et al. on the DNA encoding mouse surviving, which is identical to SEQ ID NO: 3, and the teachings of Tanabe et al. on the DNA encoding mouse CCL21, which is identical to SEQ ID NO: 7, as recited in claim 53 of instant application, into the combined teachings of Haupt et al., Gordan et al., Andersen et al., Luther et al., and Lu et al. because (i) survivin is conserved in mammals, universally expressed in tumor cells but not in other normal tissues, and SEQ ID No: 3 encodes mouse survivin, and (ii) cytokine CCL21 is known to

specifically enhance T cell mediated immune response, and SEQ ID No: 7 encodes mouse CCL21.

There would have been a reasonable expectation of success given (i) successful demonstration of DNA vaccine delivered by gene gun with an expression plasmid encoding the human calcitonin precursor preprocalcitonin enables induction of antigen-specific cellular and humoral immune responses in mice, and co-delivery of a plasmid encoding GM-CSF increased the efficacy of this DNA vaccine, by the teachings of Haupt et al., (ii) successful identification and validation of survivin as one of four universal tumor associated antigens, by the teachings of Gordan et al. and demonstration of spontaneous cytotoxic T-cell responses against survivin-derived MHC class I-restricted T-cell epitopes in breast cancer, leukemia, and melanoma patients both *in situ* as well as *ex vivo,* by the teachings of Andersen et al., and (iii) successful demonstration of the effect of CCL21 in specifically increasing T cell mediated cytolytic response, by the teachings of Luther et al., and (iv) successful generation of attenuated *Salmonella typhimurium* that can express exogenous antigens and the demonstration of using attenuated *Salmonella typhimurium* for oral vaccination, by the teachings of Lu et al., 1998, and (v) DNA construct encoding mouse survivin and DNA construct encoding mouse CCL21 were readily available by the teachings of Bennett et al. and Tanabe et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and Response to Applicant's arguments

(i) Applicant argues that to establish a *prima facie* case of obviousness, the Patent and Trademark Office bears the burden of satisfying three requirements. First, as the U.S. Supreme

Court recently held in *KSR International Co. v. Teleflex Inc.* 82 USPQ2d 1385 (2007):

> [A] court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions ....it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue .... it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.., because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." Id. at 1396

Secondly, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.,* 18 USPQ 1016, 1023 (C.C.P.A. 1970). Thirdly, all words in a claim must be considered in judging the patentability of that claim against the prior art. In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970): In addition, a reference should be considered for all that it would have fairly suggested to those of ordinary skill in the art, not just those parts that would support a conclusion of obviousness (see e.g., *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, lnc.*, 230 USPQ 416 (Fed. Cir. 1986) (See pages 4-5 of Applicant's arguments filed on 08/19/2009).

In response: With regard to the asserted requirement for teaching, suggestion, or motivation to render obviousness, the Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to

support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner also notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine Haupt et al. (2002), Gordan et al. (2002), Andersen et al. (2001), Luther et al. (2002), and Lu et al. (1998) has been clearly set forth on pages 7-14 of the office action mailed on 05/26/2009, and reiterated above in this office action.

(ii) Applicant argues that Haupt et al. provide a review of potential strategies for DNA vaccination against tumor-associated antigens for anti-tumor therapy. This reference discusses a number of advantages and difficulties associated with DNA vaccination against tumor-associated antigens. In particular, this reference points out that tumor-associated antigens are self-antigens and that it can be difficult to overcome self-antigen tolerance (see page 231, paragraph bridging col. 1 and col. 2). Another problem is that tumors tend to be heterogeneous, and not all tumor cells express the same tumor-associated antigens (see page 322, col. 1). Thus, this reference teaches that the results of targeting a given tumor-associated antigen are unpredictable. Haupt et aL point to two strategies to potentially overcome these difficulties, i.e., use of a xenogeneic source for the tumor antigen (i.e., DNA encoding a similar antigen from another species) to avoid self-tolerance, and the use of vaccines that encode more than one tumor-associated antigen to address the tumor heterogeneity issue (see conclusions beginning on page 233, second column). At page 229, col. 1 through page 230, col. 2 the reference discloses a number of methods for delivering a DNA vaccine (e.g., intravenous, intramuscular, and aerosol). Significantly, none of those methods involves oral delivery, much less oral delivery in an attenuated *S. typhimurium* vector as claimed (See page 6 of Applicant's arguments filed on 08/19/2009).

Applicant argues that the primary reference, Haupt et el., teaches that vaccinations against tumor-associated antigens is unpredictable, and that it is undesirable to directly target a single syngeneic tumor-associated antigen, as in the present claims. Haupt et el. clearly would have suggested to one of ordinary skill in the art to utilize xenogeneic tumor antigens and to target more than one antigen in order to avoid the difficulties noted in the prior art, which is contrary to the claimed invention. A reference must be considered for all that it teaches, not just that which might support a finding of obviousness. The present Office Action does not follow this admonition. The Office Action does not explain why one of ordinary skill in the art would have ignored the teachings of Haupt et el. regarding the inadvisability of targeting a single syngeneic antigen, while following other portions of the reference (See page 7 of Applicant's arguments filed on 08/19/2009).

Applicant argues that the Office Action emphasizes that survivin is one of only four alleged "universal" tumor-associated antigens, implying a finite number of choices. Haupt et al., on the other hand, highlight the unpredictable nature of vaccines targeting tumor-associated antigens, and point to strategies other than targeting "universal" antigens, so the number of potential targets available to one of ordinary skill in the art at the time of the invention was much larger than just four. In the present case, there are, in fact, a very large number of potential combinations for the tumor antigen, the cytokine adjuvant, and the delivery vehicle that will be effective for both the tumor antigen and the cytokine. The selection of all of these variants based on the applied art clearly would have involved undue experimentation. See also *Takeda Chemical Industries Ltd. v. Alphapharm Pry. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) (no identification of a predictable solution where prior art discloses a broad selection of compounds) (See page 8 of Applicant's arguments filed on 08/19/2009).

Applicant concludes that the prior art does not provide a predictable road-map to combine all of the elements of the present claims together to achieve the required CTL response without undue experimentation, prior knowledge of the present application, or inventive insight. The only road-map to the presently claimed invention of record here is the present application, itself. Applicant argues that the "obvious to try" standard upon which the Examiner appears to be relying to combine the disparate elements from the prior art is not applicable to the present claims, however, since the number of alternatives in the case of anti-tumor vaccines (choice of

potential antigens, number of antigens to target, combined with choice of cytokine and choice of vector) would have been very large, and the results would not have been predictable (see KSR, 82 USPQ2d at 1397). Applicant asserts that withdrawal of the present obviousness rejection is warranted.

In response: Applicant's arguments are focused on the deficiency of primary reference Haupt et al., (2002) and appears to totally disregard the teachings of Gordan et al. (2002), Andersen et al. (2001), Luther et al. (2002), and Lu et al. (1998). Applicant is reminded that if Haupt et al., (2002) teaches all elements of claim 1, it would have been a rejection under 35 U.S.C. 102. Claim 1 as a whole was clearly *prima facie* obvious based on the collective teachings of Haupt et al., (2002), Gordan et al. (2002), Andersen et al. (2001), Luther et al. (2002), and Lu et al. (1998).

Haupt et al., (2002) does provide a road-map, as Applicant calls it, for claimed invention in term of DNA vaccination, antigen-specific cellular immune responses (i.e. T-lymphocyte immune response recited in claim 1) can be generated, and the induction of specific immune responses directed against antigens expressed in tumor cells and displayed e.g., by MHC class I complexes can inhibit tumor growth and lead to tumor rejection (See abstract, Figure1, Haupt et al., 2002). Haupt et al., (2002) specifically teaches that a common strategy to further enhance DNA-based immunization is to employ cytokine genes as adjuvants. (See Table 1, and right column, page 230, Haupt et al., 2002) by linking the cytokine gene directly to the DNA vaccine or inserting DNA coding for an immunomodulatory peptide of a cytokine (See left column, page 231, Haupt et al., 2002). Furthermore, Haupt et al., (2002) provides successful examples for DNA vaccination against tumor antigens in animal model by various tumor associated antigens, including HER-2/neu (for breast cancer) and prostate-specific antigen (See Table II, page 232, Haupt et al., 2002).

The teachings of Gordan et al. (2002) and Anderson et al. (2001) provide specific motivation why survivin can be used in immunotherapy taught by Haupt et al. It is noted that the advantage and difficulties associated with DNA vaccination against tumor-associated antigens discussed by Haupt et al. are in no way indicating DNA vaccination against tumor-associated antigens for anti-tumor therapy is so unpredictable and without expectation of success as

Applicant argues. Applicant's arguments are certainly not true based on the successful examples reviewed by Haupt et al. (See Table II, page 232, Haupt et al., 2002). It is worth noting that an artisan reading Haupt et al. (2002) would have Anderson et al. (2001) available as a reference as Anderson et al. was published in 2001, and Anderson et al. (2001) specifically teaches cytotoxic T-cell responses against survivin-derived MHC class I-restricted T-cell epitopes in situ as well as ex vivo in cancer patients. Therefore, it would be *prima facie* obvious for a skilled artisan to substitute the tumor-associated antigens taught by Haupt et al. with the surviving taught by of Gordan et al. (2002) and Anderson et al. (2001) with the motivation to induce cytotoxic T lymphocyte immune response against all tumors.

With regard to CCL21 as an adjuvant, Luther et al specifically teaches a striking feature of the infiltrates in RIP-CCL21 transgenic mice was the localization of DCs and T cells, but not B cells, close to the chemokine-expressing islet cells., which is exactly the opposing pattern has been previously observed in RIP-CXCL13 transgenic mice, where B cells line the islets and T cells are localized more distantly (See second paragraph, left column, page 426, Luther et al., 2002). Therefore, it would be *prima facie* obvious for a skilled artisan to use CCL21 to enhance the cytotoxic T-lymphocyte immune response induced by DNA vaccine encoding survivin. Therefore, the combination of survivin and CCL21 in a DNA vaccine is based on numerous choices as Applicant argues.

Finally, with regard to "DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut", Lu et al. (1998) specifically teaches that attenuated *Salmonella typhimurium* has been proposed as one means of providing effective delivery of desired antigens, and they provide the advantage that they can be delivered orally. Lu et al. (1998) specifically states that the bacteria grow rapidly and do not require growth in cell culture. Thus, large scale production of vectors, for example, in the use of vaccines, can be accomplished more quickly and easy then where mammalian tissue cultures are required. After oral ingestion, *Salmonella* are concentrated within the liver, spleen, bone marrow, and the Peyers' patches of the gut-associated lymphoid tissue (GALT) (See Abstract, and lines 39-54, column 1, Lu et al., 1998).

Based on the discussions provided in this response, the Examiner maintains the position that the collective teachings of Haupt et al., (2002), Gordan et al. (2002), Andersen et al. (2001),

Luther et al. (2002), and Lu et al. (1998) as a whole clearly render claim 1 of instant application *prima facie* obvious.

Conclusion

6. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-

3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632